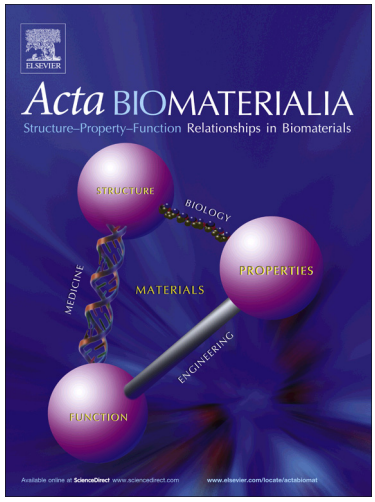

Full length article

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Cell-Laden and Orthogonal-Multilayer Tissue-Engineered Corneal Stroma Induced by a Mechanical Collagen Microenvironment and Transplantation in a Rabbit Model

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Abstract The development of functional therapies for corneal repair and regeneration is a pressing issue. Corneal stroma provides the principal functions of the cornea. However, because of the highly organized nature of the stromal matrix, the attempts to reproduce corneal stroma might follow a scar model. Here, we have developed a protocol for the efficient generation of a cell-laden and orthogonal-multilayer tissue-engineered (TE) corneal stroma, which is induced by the mechanical effects of compressed collagen (CC) or stretched compressed collagen (SCC). Within SCC, with applied compression and force extension, collagen microfibres and corneal stromal cells (CSCs) are arranged orderly, while collagen fibres and CSCs in CC are randomly arranged. Dehydrated SCC has higher tensile strength than dehydrated CC. Hydrated SCC has similar transparency with hydrated native corneal stroma. Compared with those cultured on tissue culture plates (TCP), down-regulation of the genes and proteins of cytoskeleton, activation, proliferation, collagen and *TRPV4*, up-regulation of proteoglycans, gap junction proteins and *TRPA1* are in CSCs of CC and SCC. Moreover, SCC and CC grafts displayed biocompatibility and integration with host corneal tissue after rabbit intra-corneal stromal transplantation by wk 6 under slit lamp microscopy, *in vivo* confocal microscopy and histological examination. The SCC model facilitates the construction of physiological feature TE corneal stroma, which serves as a foundation for physiological TE construction of other tissues.

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